

and adding excess of sodium borohydride in aqueous medium. The resulting yellow orange compound is diluted with water and the compound is extracted with petroleum ether. The petroleum extracts are washed with water and then dried, which results in crystallized form of reduced coenzyme Q₁₀, the pure hydroquinone of coenzyme Q₁₀. This may be a recrystallized form, alcohol-petroleum ether mixture. The Examiner also points out that applicants' specification acknowledges that impurities are present in the reduced coenzyme Q₁₀, impurities such as oxidized coenzyme Q₁₀, reducing agents such as sodium borohydride, and other known reducing agents such as zinc and vitamin C species. According to the Examiner, the sole difference between the invention of Claims 1-19 and Merck & Co. is that the claimed process comprises washing crystals with water-soluble organic solvents to, thereby, remove water-soluble impurities from the crystals while, in contrast, the Merck & Co. process involves washing petroleum extract with water and the product is then dried to obtain pure crystals.

It is admitted by the Examiner that Merck & Co. does not employ the solvents of Claims 1-19. However, the Examiner contends, it is a common practice to use suitable solvents in washing and purifying the crystals. For example, the Examiner argues that Kijima et al. (US 4,061,660) teach washing of crystals with diethyl ether (see Example 1), Kijima et al. (US 4,039,573), discloses an analogous washing process where zinc is the catalyst (see Example 3) and Morita et al. (US 4,163,864) utilizes an analogous process where methanol is used for washing (see Example 1).

In summary, the Examiner has concluded that since Merck & Co. teaches preparation and purification of reduced coenzyme Q₁₀ from the oxidized form of coenzyme Q₁₀ in ethanol while adding an excess of sodium borohydride, and the applicants' specification

acknowledges that impurities are present in the reduced coenzyme Q₁₀ while the Kijima et al. and Morita et al. prior art teach the use of water soluble organic solvents in washing the crystals to remove the impurities, it would have been obvious to one of ordinary skill in the art of the time of the invention was made to start with the Merck and Co. teachings and combine the teachings of known solvents for the purification process to achieve the applicants' Claims 1-19 with a reasonable expectation of success. After all, the Examiner contends, it is a simple process of washing to remove impurities using suitable solvents, and the selection of a solvent depends simply on the solubility of the impurities. According to the Examiner, modifying such parameters would be prima facie obvious because an ordinary artisan would be motivated to optimize the purification process to make the process more economical, since it is within the scope to exchange the solvents through a routine experimentation. Applicants submit that this argument has fatal flaws, however, as the following rationale proves.

Regarding the use of so-called, "known solvents", the Examiner contends that Kijima et al. (US 4,061,660) teach washing of crystals with diethyl ether. But the Examiner's contention must be based on a misunderstanding. The misunderstanding is based on Example 1, column 4, line 50 to 51 in that reference. In the filtration step there, the reaction product coenzyme Q₁₀ analogue was recovered as filtrate in which coenzyme Q₁₀ analogue was dissolved in the reaction mixture. The solid matter which remained on the filter was residue of silica-alumina which had been used in the reaction. In other words, the washing disclosed in Example 1 of Kijima et al. '660 is a step for rinsing the silica-alumina residue of recovered reaction mixture adhered on the residue for the purpose of increasing recovery of

the target product. Thus, washing of crystals of a target product is not disclosed in the Kijima et al. '660 reference.

Regarding Kijima et al. (US 4,039,573), Example 3, and Morita et al. (US 4,163,864), Example 1, on the other hand, each reference discloses washing of filtrate of reaction mixture with water or methanolic aqueous sodium hydroxide solution. Once again, washing of crystals of a target product is not disclosed.

The secondary references relied upon disclose only washing of a solution containing organic solvents. The present invention relates to the washing of crystals or oily forms of reduced coenzyme Q₁₀. The secondary references do not teach any of washing crystals or oily form of reduced coenzyme Q₁₀.

In addition to the aforescribed shortcomings of these secondary references, it should be apparent that the selection of water-soluble organic solvents, which are used in the present invention for removing water soluble impurities, would not be obvious to a person skilled in the art at the time of the invention. A person skilled in the art would not be expected at the time of the invention to recognize that a water soluble organic solvent would be more effective for removing water soluble impurities than water. In that regard, a person skilled in the art would normally select water as a solvent suitable for removing water soluble impurities, because the selection of a solvent depends on the solubility of the impurities, as the Examiner says (see page 4, lines 12 to 13 in the Office Action), and water is most effective for removing water soluble impurities in view of solubility. On the other hand, the present invention was made based on the unexpected effect that water soluble organic solvents are most effective for removing water soluble impurities. A person skilled in the art would not expect that.

Applicants respectfully submit that the outstanding rejection is founded on a hindsight assembly of references in a manner which would not have been recognized by the Examiner (or those skilled in the art) except for the teaching of the applicants. Amended Claim 1 is the only independent claim in the application. Applicants contend, for the foregoing reasons, that Claim 1 (and its dependent Claims 2-18) do not define obvious subject matter and that the application should be passed to issue.

Respectfully submitted,

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